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Lateralized deficit of response inhibition in early-onset schizophrenia

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ABSTRACT

Background. The ability to inhibit inappropriate or unwanted actions is a key element of executive control. The existence of executive function deficits in schizophrenia is consistent with frontal lobe theories of the disorder. Relatively few studies have examined response inhibition in schizophrenia, and none in adolescent patients with early-onset schizophrenia (EOS).

Methods. Twenty-one adolescents with the onset of clinically impairing psychosis before 19 years of age and 16 matched controls performed a stop-signal task to assess response inhibition. The patients with EOS were categorized as paranoid ($n=10$) and undifferentiated subtypes ($n=11$). The undifferentiated group had higher levels of negative symptomatology. Stop-signal reaction time (SSRT) and go-signal reaction time (Go-RT) were analysed with respect to hand of response.

Results. The undifferentiated early-onset patients had significantly longer SSRTs, indicative of poor response inhibition, for the left hand compared to the paranoid early-onset patients and control participants. No differences existed for inhibitory control with the right hand. The three groups did not differ in Go-RT.

Conclusions. Our results indicate a specific lateralized impairment of response inhibition in patients with undifferentiated, but not paranoid, EOS. These findings are consistent with reports of immature frontostriatal networks in EOS and implicate areas such as the pre-motor cortex and supplementary motor area (SMA) that are thought to play a role in both voluntary initiation and inhibition of movement.

INTRODUCTION

Executive dysfunction is a prominent feature of schizophrenia (Kolb & Wishaw, 1983; Berman *et al.* 1986; Pantelis *et al.* 1997). The existence of executive deficits in schizophrenia is consistent with frontal lobe theories advanced by Kraepelin (1913) and Bleuler (1911), and confirmed by modern neuroimaging techniques (Berman *et al.* 1986; Buchsbaum *et al.* 1992; Hill *et al.* 2004; Kumra *et al.* 2004). Executive function comprises distinct aspects of response inhibition, working memory, set-shifting and interference control (Pennington & Ozonoff, 1996; Miyake *et al.* 2000). Although deficits in working memory, set-shifting and interference control are well established in schizophrenia, relatively few studies have examined response inhibition (Kiehl *et al.* 2000; Weisbrod *et al.* 2000; Rubia *et al.* 2001*a*; Badcock *et al.* 2002; Ford *et al.* 2004). It remains controversial whether cognitive deficits are more pronounced in those patients with a relatively earlier onset of schizophrenic illness (Kravariti *et al.* 2003*b*;

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Pantelis *et al*. 2003). The objective of this paper was therefore to examine response inhibition in patients with early-onset schizophrenia (EOS).

Although the cognitive mechanisms underlying response inhibition have been studied within cognitive psychology for many decades (Logan & Cowan, 1984; Logan, 1994; Logan *et al*. 1997), it is only relatively recently that the neural basis of inhibitory control in the human brain has been investigated. Human lesion and neuroimaging studies support the view that response inhibition is achieved throughout a neural network including the inferior (IFG) and middle frontal gyri (MFG), supplementary motor area (SMA) and the inferior parietal lobule (Garavan *et al*. 1999; Rubia *et al*. 2001*b*; Aron *et al*. 2003). Activation foci may also be seen in midline regions, such as the anterior cingulate (Rubia *et al*. 2001*b*), although such activations may reflect ancillary processes such as monitoring response conflict (Carter *et al*. 1998) or error detection (Garavan *et al*. 2003), rather than response inhibition *per se*. Human lesion (Aron *et al*. 2003), split brain (Funnell *et al*. 2004), transcranial magnetic stimulation (TMS) (Chambers *et al*. in press) and functional imaging studies all suggest a dominant role of the right hemisphere, particularly the IFG, in response inhibition (Konishi *et al*. 1998; Garavan *et al*. 1999; Ford *et al*. 2004; Kelly *et al*. 2004).

Relatively few studies have examined response inhibition in schizophrenia (Kiehl *et al*. 2000; Weisbrod *et al*. 2000; Rubia *et al*. 2001*a*; Badcock *et al*. 2002; Ford *et al*. 2004) and results are conflicting. The majority of these studies have used classic go/no-go paradigms in which a response to an infrequent target stimulus (the no-go stimulus) must be withheld. Typically, prepotency to the go-stimulus is established by presenting many more go stimuli than no-go stimuli. Of those studies using go/no-go paradigms with schizophrenia and control groups, two have reported no behavioural differences (Fallgatter & Muller, 2001; Rubia *et al*. 2001*a*), two have reported impaired response inhibition in schizophrenia (Kiehl *et al*. 2000; Weisbrod *et al*. 2000), and one has reported superior inhibitory performance in patients with schizophrenia (Ford *et al*. 2004).

Electrophysiological studies of response inhibition in schizophrenia are also inconclusive, with the N2 component, for example, reduced in some studies (Kiehl *et al*. 2000) but not in others (Weisbrod *et al*. 2000; Ford *et al*. 2004). Neuroimaging studies find intact inhibitory performance despite reduced activation in the left anterior cingulate and rostral dorsolateral prefrontal cortex (Rubia *et al*. 2001*a*). Alternatively, decreased activation in right frontal and parietal regions has been reported (Ford *et al*. 2004). Inconsistencies may have arisen for several reasons. First, the go/no-go paradigm is susceptible to changes in response criteria over time, or between participants. Failure to establish the prepotent go-response may therefore reflect a strategic performance difference and a cautious response style (compared with Ford *et al*. 2004). Second, differences in the clinical samples also make interpretation difficult. For example, Rubia *et al*. (2001*a*) recruited patients with a recent illness onset, whereas others recruited patients with chronic illnesses (Weisbrod *et al*. 2000; Fallgatter & Muller, 2001; Ford *et al*. 2004). Generalized slowness in the latter group could confound performance on go/no-go tasks.

The stop-signal paradigm

An alternative paradigm for the investigation of response inhibition is the stop-signal paradigm. In this task, an established pattern of responding to a go-signal must be inhibited upon presentation of a countermanding stop-signal. Typically the go-task involves a choice–reaction-time (CRT) decision, requiring, for example, left and right button presses upon presentation of the letters 'X' and 'O' respectively (Logan *et al*. 1997). The stop-task, typically occurring in 25% of trials, signals participants to withhold their response to the go-signal. Instructions typically emphasize speed of responding, and successful inhibition can therefore be conceptualized as a race between competing go- and stop-processes.

The main dependent variable in the stop-signal paradigm is the stop-signal reaction time (SSRT). The SSRT is measured by introducing a stop-signal delay (SSD) between the presentation of the go- and stop-signals, so that the latency of the stop-process can be measured indirectly. SSDs are either selected randomly from a fixed array (method of constants; Logan & Cowan, 1984) or varied dynamically

contingent upon the response of the participant (method of limits; Osman *et al.* 1986; Kornblum *et al.* 1990; Logan *et al.* 1997). The SSD at which the participant can successfully inhibit 50% of the stop-trials represents the amount of processing time required to tie the race between the go- and stop-processes (Osman *et al.* 1986; Kornblum *et al.* 1990). As this delay represents the average point in time of the completion of the stop-process, it can be used to estimate the SSRT. The SSRT can be derived as the difference between the mean go-signal RT (Go-RT) and the delay at which the participant inhibits correctly on 50% of stop-signal trials (Osman *et al.* 1986, 1990; Logan, 1994; Logan *et al.* 1997).

Badcock *et al.* (2002) used the stop-signal paradigm in patients with schizophrenia, a psychosis comparison group and healthy controls. To control for shifts in response criteria, they adopted a method of constants and set six SSDs relative to each subject's own Go-RT. Although the groups did not differ in terms of their SSRT, the relationship between SSD and inhibitory performance was significantly flatter in the schizophrenia group compared to the psychosis group or the healthy controls. Badcock and colleagues argued that in schizophrenia there is an inability to trigger the inhibitory act, as indicated by a flatter inhibition function, but that once this act was triggered, the speed of inhibition was comparable to that of the control groups.

The present study sought to extend the previous literature in two important ways. First, we recruited a sample of adolescents with early-onset schizophrenia (EOS), that is an onset of schizophrenic illness prior to 19 years of age (Bellgrove *et al.* 2003, 2004). Although early- and adult-onset forms of the disorder may share the same pathophysiological substrates (Hollis, 2000; Nicolson *et al.* 2000), EOS may be characterized by a relative neurodevelopmental delay. Specifically, adolescents with EOS are developmentally delayed prior to the onset of psychosis (Hollis, 1995) and may show a persistence of neurological soft signs (Karp *et al.* 2001). Using diffusion tensor imaging, Kumra *et al.* (2004) reported reduced white matter integrity in the frontal lobes, including the IFG, of adolescents with EOS. Dysfunction within the IFG has been suggested as the pathophysiological substrate of negative symptoms in schizophrenia (Wolkin *et al.* 2003). These lines of evidence suggest that immaturity of frontostriatal neural networks (James *et al.* 2004), including the IFG, might confer vulnerability to an early onset of schizophrenia. We assayed the functional integrity of inhibitory networks in EOS using a stop-signal task. We predicted that inhibitory deficits would be most pronounced in those patients with higher negative symptoms.

Second, we applied an adaptive psychophysical staircase method to the problem of estimating the 50% correct inhibition threshold. Adaptive staircase methods are highly applicable to the estimation of the inhibition threshold because they place most observations close to threshold (Levitt, 1971). Furthermore, most previous studies have examined inhibitory performance within the stop-signal paradigm without regard to response hand (Logan & Cowan, 1984; Osman *et al.* 1986, 1990; Logan *et al.* 1997). Arguments have been made, however, that motor areas such as the SMA may play a role in both initiating and inhibiting voluntary action (Badcock *et al.* 2002). As each laterality is controlled by motor areas in the contralateral hemisphere, hand of response may be an important factor to consider in response inhibition. This may be particularly germane to schizophrenia, where anomalies of motoric areas have been observed (Dreher *et al.* 1999; Payoux *et al.* 2004; Rogowska *et al.* 2004). The present study therefore used for the first time two independent, interleaved staircases to assess inhibitory control as a function of response hand in adolescents with EOS.

METHOD

Participants

Adolescents with early-onset adolescent schizophrenia and healthy controls participated in this study. Written informed consent was provided by the participant or the parent of the participant.

Twenty-one adolescent patients (12 male) with a diagnosis of EOS (DSM-IV; APA, 1994) were recruited from in- and out-patient adolescent units in metropolitan Melbourne, Australia. Patients were defined as being of adolescent early-onset if clinically impairing

psychotic symptoms first appeared after the age of 12 but before 19. Patients were diagnosed categorically through a semi-structured clinical interview using DSM-IV criteria (K-SADS-PL; Kaufman *et al.* 1999) and dimensionally through the Positive and Negative Symptom Scale (PANSS; Kay *et al.* 1987).

The EOS group had a mean PANSS positive scale score of 21 (S.D. = 5·6) (60th percentile), a mean negative scale score of 26 (S.D. = 5·9) (75th percentile), a mean general psychopathological scale score of 53 (S.D. = 11·5) (90th percentile), and a mean total symptom score of 100 (S.D. = 21·5). Patients were categorized according to DSM-IV subtype: 10 of these participants were diagnosed as having paranoid EOS while 11 were diagnosed as having undifferentiated EOS. The undifferentiated group had higher scores on the negative scale of the PANSS than the paranoid group [$t(18) = 2{\cdot}1$, $p = 0{\cdot}05$] but did not differ on the other dimensions.

The paranoid EOS group had a mean age of 16·9 years (S.D. = 1·7) and the undifferentiated EOS group had a mean age of 13·9 years (S.D. = 2·5). Participants were administered the age-appropriate Wechsler Standardized Achievement Test; the paranoid and undifferentiated groups exhibited IQs within the average range (paranoid EOS: mean IQ = 96, S.D. = 12·8; undifferentiated EOS: mean IQ = 100, S.D. = 13·7). Fifteen of the patients were unmedicated and the remaining six were taking atypical neuroleptics at the time of testing, with equal numbers of medication naive and medicated participants in the paranoid and undifferentiated EOS groups. All of the paranoid EOS patients were right-handed as determined by a handedness questionnaire (Patterson & Bradshaw, 1975), while 10 of the 11 undifferentiated EOS patients were right-handed. Participants had normal or corrected-to-normal vision and no colour blindness.

A group of 16 control participants (11 male, 13 right-handed) was recruited from the general community and from Rossbourne Secondary College, Hawthorn, Melbourne. These subjects were free of neurological or psychiatric disturbance, had a mean age of 15·9 years (S.D. = 1·7) and a mean IQ of 99·6 (S.D. = 10·3). The three participant groups (paranoid EOS *versus* undifferentiated EOS *versus* controls) did not differ in terms of IQ [$F(2, 34) = 0{\cdot}38$, $p > 0{\cdot}05$] but did differ in age [$F(2, 34) = 6{\cdot}52$, $p < 0{\cdot}05$], with the undifferentiated EOS patients being younger than both the paranoid EOS patients and controls.

Apparatus and procedures

Participants sat in front of an active-screen Toshiba Satellite Pro 4300 portable computer, with the screen centred on their sagittal midline. Participants rested the index fingers of their left and right hands on two response buttons, fixed within a response box. Responses were executed by pressing one of the buttons as quickly and as accurately as possible. Reaction times (RTs) were recorded to the nearest millisecond (ms).

Participants performed a stop-signal task, similar in nature to that described by other authors (Logan *et al.* 1997). The experiment used a simple one-up one-down adaptive staircase method to estimate the SSD for the 50% inhibition threshold. This procedure has the advantage of placing most observations near the 50% point, thereby increasing the power and efficiency of the experiment (Levitt, 1971). The increments by which the onset (i.e. SSDs) of the stop-signal are either increased or decreased are called steps.

The step-size of the SSDs was tied to the standard deviation (S.D.) of the participant's RT distribution for Go-responses defined in a pre-experimental phase (see below). Calibrating the step-size to the participant's Go-RT distribution has several advantages. First, the pattern of step-size adjustments is subjectively equivalent for all subjects, which should equalize the difficulty of the task both within and between the patient and control groups. This manipulation should minimize error variance and maximize statistical power. Second, this method increases the efficiency of the adaptive staircase by using a final step-size tailored for that participant's psychometric function (i.e. it will not be too small and therefore inefficient, or too large and therefore inaccurate). Finally, our approach aims to homogenize criterion shifts (slowing of Go-RT to inhibit upon more occasions) that could unduly influence the value of the 50% correct inhibition point across participants.

The following section describes the procedures used for all participants leading to the estimation of the 50% correct inhibition point and calculation of the SSRT. The experiment

consisted of three phases: a practice phase, a pre-experimental phase, and an experimental phase.

Practice phase

Participants completed 20 practice trials. The Go-stimuli were an uppercase 'X' or 'O', yellow on a black background, presented centrally for 1000 ms or until a response was executed. The 'X' was 27 mm in height and 25 mm in width (visual angles 3·09° and 2·86° respectively) and the 'O' was 29 mm in height and 28 mm in width (visual angles 3·32° and 3·21° respectively). The 'X' was mapped to a left response and the 'O' to a right response. A 500 ms fixation point, followed by a variable screen blank (200–1000 ms), preceded the presentation of the Go-stimulus. Equal numbers of the Go-stimuli were presented in a random order (i.e. 10 X's and 10 O's), with the stop-signal presented randomly on 25% of occasions. The stop-signal was a 100 ms, 1000 Hz tone presented through an external speaker attached to the response apparatus. SSD was varied randomly between 0 and 400 ms. Once initiated, trials proceeded continuously. Participants were instructed to respond to the Go-stimuli as quickly as possible and to inhibit responding when they heard the tone. The requirement for speed of response was reinforced in the practice session by computer-generated feedback (accuracy and RT) provided between trials, which encouraged the participant to 'go faster'.

Pre-experimental phase

The pre-experimental phase comprised 200 trials presented in four blocks of 50, and was designed to establish the participant's Go-RT distribution and yield the S.D. of this distribution for setting the staircase step-size in the experimental phase. This phase proceeded in the same manner as the practice phase, with the exception that the feedback regarding the correct response was withdrawn. Stop-trials were presented randomly on 25% of occasions with the SSD varied randomly between 0 and 400 ms. Speed of responses was again emphasized by the experimenter.

Experimental phase

In the experimental phase, the S.D. of each participant's Go-RT distribution from the pre-experimental phase was used to set the step-size for an adaptive staircase to estimate the 50% inhibition threshold.

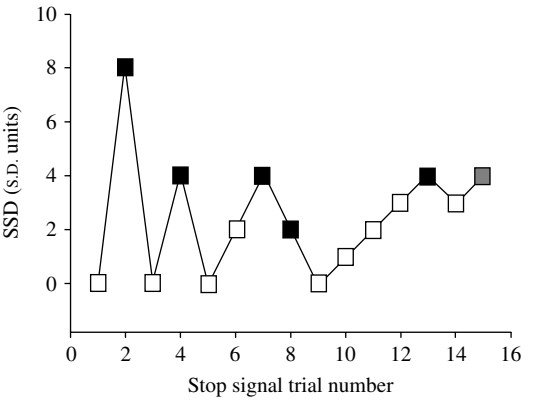

FIG. 1. A hypothetical staircase track adopting the 50% adaptive method. Black squares represent a correctly inhibited stop-trial, white squares represent a failed inhibition on a stop-trial, and the grey square represents the threshold value (S.D. units) or 50% correct inhibition point. Note that the first stop-signal is coincident with the go-signal (SSD = 0). The second stop-signal, assuming correct inhibition on the first, was presented at a delay of 8×S.D. Thereafter the staircase followed a one-up one-down staircase.

Setting the step sizes

From an initially tested SSD of 0, the step-size (ms) was increased to a large multiple of the participant's Go-RT S.D. ($8 \times$ S.D.) (see Fig. 1). Correct inhibition at this maximum SSD was permitted only five times before the session was terminated. This procedure safeguarded against extreme criterion shifts that could occur across the testing session. Following a failed inhibition, the next stop-trial was presented at the most recently correctly inhibited SSD. If the response was correctly inhibited twice running, then the step-size was halved (in S.D. units) and the SSD increased by the corresponding step-size (ms). Step-size (in S.D. units) was therefore halved after two correct inhibitions at the same SSD. Trials continued until a failed inhibition occurred at the minimum step-size. The minimum step-size was determined by halving the S.D. eight times. The 50% correct inhibition point was then taken as the SSD (ms) at which the last correct inhibition occurred.

Independent adaptive staircases for left and right responses

As it was of interest whether response inhibition varied as a function of response hand, two

Table 1. *Definitions for each of the four possible response types within the stop-signal paradigm*

Error type	Definition
Incorrect responses	Incorrect response on a Go-trial
Incorrect failed inhibition	Incorrect response and a failed inhibition on a Stop-trial
Missed trials	Missed detection on a Go-trial
False alarm	Correct response on a Go-trial but sooner than 100 ms

adaptive staircases were administered independently for left and right responses. This was achieved by setting step-sizes separately for each of the left and right responses, based upon the S.D. of the Go-RT distributions established for each hand in the pre-experimental phase. When the 50% correct inhibition point for one hand was reached prior to that of the other, all remaining stop-trials for the completed laterality were presented with an SSD equal to this obtained value, until the inhibition threshold of the other hand was reached.

The experimental phase proceeded in blocks of 50 trials until the participants had reached their 50% correct inhibition point for both hands. During this phase, speed of response was emphasized, and participants received a 'Go Faster' prompt if their Go-RT for a response slowed to greater than the longest correct Go-RT of the respective hand from the pre-experimental phase. Preliminary analysis indicated that the Go-RT distributions for each of the two groups did not differ statistically between the pre-experimental and experimental phases.

Treatment of errors and outliers

Incorrect responses (e.g. pressing the wrong button on a Go-trial) did not contribute to the Go-RT distributions in either the pre-experimental or experimental phases. Step-size adjustments were implemented only after a correct or failed inhibition. During the experimental phase, all instances of errors were recorded for subsequent analysis. Four different response types were possible (Table 1). In both the pre-experimental and experimental phases, correct Go-RT values $\pm$ three standard deviations were excluded from the analysis.

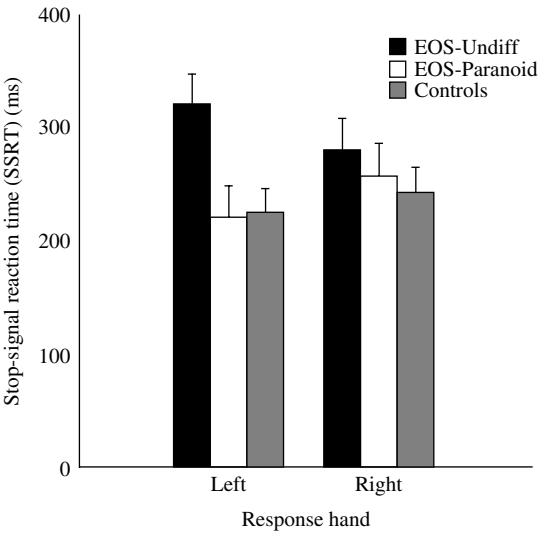

FIG. 2. Stop-signal reaction time (SSRT) (ms) for left and right response hands for each of the early-onset schizophrenia (EOS) and control groups. Undiff, Undifferentiated subtype.

RESULTS

Analysis of SSRT

SSRT was calculated by subtracting the SSD corresponding to the 50% inhibition threshold from the mean Go-RT (Logan *et al.* 1997). This calculation was performed separately for each hand. As mean age differed across groups, it was important to determine the relationship between age and SSRT, as a function of hand of response. Partial correlations between age, left-hand SSRT and right-hand SSRT (controlling for group) revealed no significant correlations (all r's $< 0{\cdot}13$). Accordingly, we conducted a group (paranoid EOS *versus* undifferentiated EOS *versus* controls) by response hand (left *versus* right) mixed-model analysis of variance (ANOVA) on the SSRTs. There were no main effects of response hand [$F(1, 34) = 0{\cdot}25$, $p = 0{\cdot}62$] or group [$F(2, 34) = 2{\cdot}43$, $p = 0{\cdot}10$]. There was a significant interaction between group and response hand [$F(2, 34) = 3{\cdot}74$, $p = 0{\cdot}03$, $\eta^2 = 0{\cdot}18$] (Fig. 2). Bonferroni comparisons revealed that this interaction was driven by the significantly longer SSRT of the undifferentiated EOS group with the left hand, relative to that of both the control ($p = 0{\cdot}03$) and paranoid EOS ($p < 0{\cdot}04$) groups. There was no significant difference between the control and

Table 2. *Mean percentage error rates and standard deviations for the early-onset patient groups and the control group, for each of incorrect, incorrect failed inhibitions, missed trials, and false alarm error types*

	Error type			
	Incorrect responses	Incorrect failed inhibitions	Missed trials	False alarm
Controls	3·4 (2·9)	0·5 (0·7)	0·4 (0·6)	0·3 (0·4)
EOS-Undiff	3·9 (2·2)	0·6 (0·6)	2·4 (2·8)	0·4 (0·8)
EOS-Paranoid	4·4 (3·3)	0·9 (0·9)	0·3 (0·5)	0·2 (0·4)
Overall	3·8 (2·8)	0·7 (0·7)	0·9 (1·8)	0·3 (0·6)

Refer to Table 1 for definitions of error types.
Values are mean (S.D.).
EOS-Undiff, Early-onset schizophrenia undifferentiated; EOS-Paranoid, early-onset schizophrenia paranoid.

paranoid EOS groups in terms of the SSRT for the left hand ($p > 0{\cdot}05$). The undifferentiated EOS group tended to have longer SSRT with the left hand compared to the right ($p = 0{\cdot}06$); however, no response hand differences existed for each of the paranoid EOS and control groups. There were no significant differences between the three groups in terms of SSRT for the right hand.

Analysis of Go-RT

To determine the relationship between mean Go-RT and age we performed partial correlations, adjusting for group. There were significant correlations between age and mean left Go-RT and mean right Go-RT [all r's $> 0{\cdot}47$ ($r^2 = 0{\cdot}22$)]. Accordingly, we conducted a group by response hand mixed-model ANOVA on mean Go-RT, co-varying for the effects of age. This analysis revealed no main effects of response hand [$F(1, 33) = 0{\cdot}259$, $p = 0{\cdot}614$] or group [controls: 416 ms (S.D. = 90); undifferentiated EOS: 504 ms (S.D. = 106); paranoid EOS: 382 ms (S.D. = 47)] [$F(2, 33) = 1{\cdot}748$, $p = 0{\cdot}190$], nor any interaction between these factors.

Error analyses

Percentage error rates were calculated for four different error types, including incorrect responses, incorrect failed inhibitions, missed trials and false alarms (see Table 1 for definitions). Percentage error rates as a function of group are presented in Table 2. Preliminary analysis revealed a significant correlation between age and false alarms only (controlling for the effect of Group) ($r = -0{\cdot}43$, $r^2 = 0{\cdot}18$, $p = 0{\cdot}01$). A significant group difference emerged only for missed trials [$F(2, 34) = 6{\cdot}632$, $p = 0{\cdot}004$]. *Post-hoc* analysis with Bonferroni corrections revealed that the undifferentiated EOS group had higher missed trial error rates than either the control ($p < 0{\cdot}05$) or paranoid EOS group ($p < 0{\cdot}05$), while the paranoid EOS and control groups did not differ ($p > 0{\cdot}05$). A partial correlation (controlling for group) revealed a significant relationship between percentage missed trials and left-hand SSRT ($r = 0{\cdot}45$, $r^2 = 0{\cdot}20$, $p = 0{\cdot}006$) and a trend for a significant correlation between percentage missed trials and right-hand SSRT ($r = 0{\cdot}31$, $r^2 = 0{\cdot}09$, $p = 0{\cdot}065$).

DISCUSSION

This study demonstrates a specific lateralized deficit of response inhibition in adolescents with EOS and high rates of negative symptoms. Specifically, undifferentiated patients had higher negative symptoms than their paranoid counterparts and exhibited prolonged SSRTs when responding with their left, but not right, hand. Furthermore, undifferentiated patients made more errors of omission than either the paranoid patients or the controls, potentially indicating a sustained attention deficit. Importantly, response inhibition deficits in the undifferentiated sample existed in the face of normal response speed, suggesting a dissociation between response inhibition and execution.

Dysfunction to the IFG may be a pathophysiological substrate of negative symptoms in schizophrenia (Wolkin *et al.* 1992). Levels of negative symptoms may also be higher in patients with relatively earlier illness onsets (Hoff *et al.* 1996). Kumra *et al.* (2004) used diffusion tensor imaging to assay white matter integrity in patients with EOS. Relative to control participants, adolescents with EOS had significantly reduced fractional anisotropy in bilateral frontal white matter, particularly in the vicinity of the IFG. Reduced anisotropy within the IFG has also been related to higher levels of impulsivity in adult patients with schizophrenia (Hoptman *et al.* 2004). These lines of evidence suggest that dysfunction within the right IFG

may be an attractive neural substrate for the response inhibition deficits observed here in patients with undifferentiated EOS.

Although converging evidence from human lesion and functional neuroimaging studies suggests a crucial role for the right IFG in response inhibition (Garavan *et al.* 1999; Aron *et al.* 2003), there is little evidence to suggest that dysfunction within this region can lead to the type of lateralized impairment in response inhibition that we observed in undifferentiated EOS (see Konishi *et al.* 1998). In fact, using the stop-signal paradigm, we have recently demonstrated that temporary neural disruption caused by TMS of the right IFG impairs response inhibition for both hands in healthy subjects (Chambers *et al.* in press). We suggest, therefore, that lateralized impairments in response inhibition may arise from dysfunction within motor control areas, such as the SMA and pre-motor cortex, that have been implicated in both response inhibition (Rubia *et al.* 2001*b*; Watanabe *et al.* 2002) and schizophrenia (Dreher *et al.* 1999; Payoux *et al.* 2004; Rogowska *et al.* 2004). It should be noted that dysfunction to either the left (Flor-Henry, 1976) or right hemisphere (Cutting, 1992) has been suggested in schizophrenia.

Our study is the second to use the stop-signal paradigm in schizophrenia (Badcock *et al.* 2002) and the first to report an interaction between diagnostic subtype and response hand. Rubia *et al.* (2001*a*) used a stop-signal paradigm within a functional imaging design, but their paradigm included only a single stop-signal delay. In their study the stop-signal occurred 250 ms after the go-stimulus on 30% of trials. Most previous studies, basic and applied, that have used the stop-signal paradigm have averaged across hand of response and may therefore have overlooked lateralized impairments. Working with an adult cohort of patients with chronic schizophrenia, Badcock *et al.* (2002) reported normal SSRT relative to psychosis and healthy control groups, but an impaired ability to initiate inhibitory acts. Without including diagnostic subtype as a factor, the current study would also have found no group effect on SSRT. In this respect our study is also compatible with previous reports of unimpaired response inhibition in adult-onset schizophrenia, broadly defined (Fallgatter & Muller, 2001; Rubia *et al.* 2001*a*). Our results therefore extend this work by demonstrating an interaction between diagnostic subtype and response hand.

The increased proportion of omission errors made by the undifferentiated EOS group is indicative of a sustained attention deficit. Sustained attention deficits are reliably observed in schizophrenia and may be a familial marker of schizophrenia (Cornblatt & Malhotra, 2001). Imaging studies of sustained attention in drug naïve patients and those experiencing prodromal symptoms of the disorder show functional deficits in the inferior frontal gyrus (Ojeda *et al.* 2002; Morey *et al.* 2005). The overlapping neuroanatomical substrates of sustained attention and response inhibition may suggest a functional link between these processes.

Maturational delays in the development of the brain are thought to confer susceptibility to an early illness onset in adolescents with schizophrenia. Supporting evidence for this hypothesis comes from studies reporting delays in cognitive, linguistic and social development (Hollis, 1995) and the persistence of neurological soft signs at a developmentally inappropriate age (Karp *et al.* 2001). Neuroimaging has begun to provide preliminary evidence for this hypothesis, with pronounced structural changes in the frontal lobe of EOS that appear larger than those in comparable studies of adult-onset patients (James *et al.* 2004). In addition, however, comparable changes in frontal microstructure have been reported across early-onset (Kumra *et al.* 2004) and adult-onset samples (Buchsbaum *et al.* 1998; Lim *et al.* 1999). The application of neurocognitive measures with known brain–behaviour relationships, such as response inhibition, may provide an additional and important source of information. In this context, the observation of a lateralized impairment in response inhibition in EOS is an important finding. Promising candidates for future functional imaging studies may be the roles of the IFG, SMA and pre-motor cortex in response inhibition, particularly in early-onset patients with high levels of negative symptomatology.

Given the low prevalence of EOS, this study was probably underpowered. The difference between the SSRTs, irrespective of hand of response, of the undifferentiated EOS group

and both the paranoid EOS and control groups were of large effect size (Cohen's $d = 0{\cdot}74$ and 0·72 respectively). This suggests that larger sample sizes are likely to reveal both main effects of diagnostic group on SSRT and an interaction between diagnostic group and hand of response. These results would then be indicative of a broad disruption to inhibitory networks in undifferentiated EOS, including the right IFG and associated regions such as the pre-motor cortex/SMA that are thought to play a role in both motoric initiation and inhibition.

In summary, we have identified a specific lateralized deficit of response inhibition in EOS. As we did not observe any group differences for response speed, our results are unlikely to reflect a generalized cognitive impairment. Instead, our findings add to a developing literature on neurocognitive deficits in EOS (Bellgrove *et al.* 2003, 2004; Kravariti *et al.* 2003*a*; McClellan *et al.* 2004; Tuulio-Henriksson *et al.* 2004). An important goal for future studies will be to determine whether response inhibition deficits may serve as a marker for vulnerability to an early onset of schizophrenia.

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DECLARATION OF INTEREST

None.

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